Chem Sci Trans., 2012, **1(2),** 335-340
DOI:10.7598/cst2012.219

Chemical Science Transactions
ISSN/E-ISSN: 2278-3458/2278-3318

RESEARCH ARTICLE

Synthesis and Crystal Structure Analysis of Ethyl-4-(4-acetoxy-phenyl)-3-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate

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Received 30 May 2012 / Accepted 15 June 2012

Abstract: 4-(4-Acetoxy-phenyl)-3-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**2**) was synthesized by a two step reaction process. Preliminary spectroscopic analysis was done by IR, ^{1}HNMR and elemental analysis. The crystal and molecular structure was further confirmed using single crystal x-ray diffraction. The dihedral angle between the planes of the aryl and dihydropyrimidine rings is 89.65(6)°, which is almost orthogonal. The dihydropyrimidine ring adopts twist-boat conformation. The crystal structure is stabilized by C-H…O, N-H…S and C-H…π interactions.

Keywords: Dihydropyrimidine, crystal structure, C-H…O, N-H…S and C-H…π weak interactions.

Introduction

Dihydropyrimidine-2(1H)-ones represents a heterocyclic system of remarkable pharmacological efficiency, including antiviral, antibacterial and anti-inflammatory activities. More recently dihydropyrimidines (DHPMs) have emerged as the integral backbones of several calcium channel modulators, anti-hypertensive agents. These inherently asymmetric dihydropyrimidine derivatives are not only better calcium channel blockers, but have also been extensively studied to expand the existing SAR (Structure activity relation) and to get further insight into molecular interactions at the receptor level[1-4]. The present work is a part of our research involving a series of novel dihydropyrimidine derivatives which can be potent mimics of the dihydropyridines. We report here the structure of dihydropyrimidine derivative which is a potential calcium channel blocker.

The synthesis of the compound was followed by measurement of the analytical data and subsequent spectroscopic analysis using IR and ^{1}H-NMR techniques to confirm the presence of the supposed ring system. The compound was subjected to single crystal X-ray diffraction analysis in order to confirm the molecular structure.

Experimental

Materials

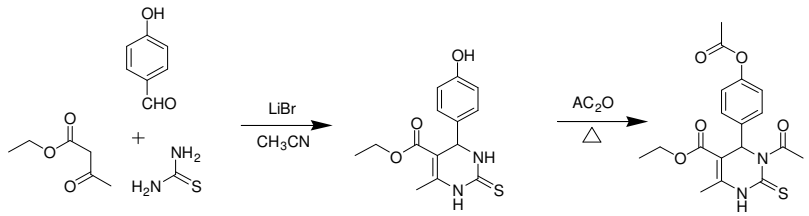
All chemicals were obtained from a commercial source and used without further purification. Pale yellow colored single-crystals suitable for X-ray diffraction were obtained by slow evaporation method using chloroform as the solvent.

Analytical methods

Melting point was determined in open capillary using Guna melting point apparatus and is uncorrected. The IR spectra were recorded on Nicolet 400D Fourier transform–infrared (FT-IR) using KBr pellets. ^{1}H NMR spectra were recorded on Bruker 300-MHz FT NMR spectrometer in $CDCl_3$ with TMS as internal standard and elemental analysis was carried out using CHNS elementar (Vario microcube). The title compound was prepared by following the procedure given below and as shown in Scheme.

*Procedure for the Preparation of the title compound (**2**)*

Compound **1** (2.0 g) was mixed with acetic anhydride (10 mL) refluxed for about 4 hours. The reaction mixture was cooled and diluted by addition of water (20 mL). The solid separated was washed with water, filtered, dried (Yield: 1.92g, 85% and mp 157 ^{0}C). Pale yellow crystals of the title compound **2** were obtained for diffraction by slow evaporation from a solution in chloroform.



1 **2**

Scheme 1. Synthesis of 4-(4-Acetoxy-phenyl)-3-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester.

Physical measurements

IR(KBr) ν cm^{-1} : 3098, 2996, 1705, 1714, 1643, 1512, 1054. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H,-CH_2CH3), 2.06 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.19 (q, J=7.2 Hz, 2H, CH_2CH_3), 5.96(S, 1H, CH), 6.92–7.56 (m, 4H, ArH) 8.32 (s, 1H, NH). %CHNS calc/found: C, 57.43/57.33; H, 5.36/5.32; N, 7.44/7.53; S, 8.52/8.41. m/z: 376.

Investigation techniques

X- ray diffraction

The X-ray diffraction data for the compound **2** was collected on a Bruker Smart CCD Area Detector System, using MoKα (λ=0.71073 Å) radiation. Intensity data was collected up to a maximum of 26.99° in the ω–ϕ scan mode. The data was reduced using SAINT-Plus[5]. The structure was solved by direct method using SHELXS97[6] and difference Fourier synthesis using SHELXL97[6]. The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97[6] and the procedures were carried out for a few cycles until convergence was reached. A total of 19001 reflections were collected, resulting in 3843 [R(int) = 0.0405] independent reflections of which the number of reflections satisfying I>2σ(I) criteria was 3130. These were treated as observed. The H atoms were placed at calculated positions in the riding

model approximation (C-H = 0.93 Å), with their temperature factors set to 1.2 times those of the equivalent isotropic temperature factors of the parent atoms. All other non-H atoms were refined anisotropically. The R factor for observed data finally converged to R = 0.0434 with wR2 = 0.1040 in the compound. The maximum and minimum values of residual electron density were 0.372 and -0.290eÅ^{-3}. Molecular diagram was generated using ORTEP[7]. The mean plane calculation was done using the program PARST[8].

Table 1. Crystal data and structure refinement of compound **2**

Empirical formula	C_{18} H_{20} N_2O_5S
Formula weight	376.42
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P ī
Unit cell dimensions	
a	7.8163(3)Å
b	9.5961(5)Å
c	12.4869(7)Å
α (°)	77.286(5)
β (°)	83.282(4)
γ (°)	76.171(4)
Volume	885.09(8) Å^3
Z,	2
Calculated density (Mg/m$^{3)}$	1.412
Absorption coefficient (mm^{-1})	0.215
F(000)	396
Crystal size	0.18 x 0.16 x 0.16 mm
Theta range for data collection	2.51 to 26.99 deg.
Limiting indices	-9<=h<=9, -12<=k<=14, -15<=l<=15
Reflections collected / unique	19001 / 3843 [R(int) = 0.0405]
Completeness to theta	26.99 99.8 %
Max. and min. transmission	0.9664 and 0.9623
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3843 / 0 / 239
Goodness-of-fit on F^2	1.000
Final R indices [I> 2sigma (I)]	R1 = 0.0434, wR2 = 0.1040
R indices (all data)	R1 = 0.0575, wR2 = 0.1119
Largest diff. peak and hole (e.A^{-3})	0.372 and -0.290

Results and Discussion

The intermediate 4-(4-acetoxy-phenyl)-3-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**1**) was synthesized by Biginelli reaction which is a one-pot, acid-catalyzed condensation reaction. Compound **1** was acylated using acetic anhydride, forming **2** (Scheme 1). Examination of analytical data of C, H, N and S content of the compound are in good agreement with calculated values based on proposed structure shown in scheme. Formation of compound **2** was confirmed by the absence of one NH and OH peak around δ 7.6 – 10.3 ppm and appearance of two singlets for 6H at δ 2.06, 2.19 ppm in the ^{1}H NMR spectra. It was further confirmed by a sharp peak at 3251cm^{-1} in the IR spectrum due to the presence of another free NH group.

Crystallography

Summary of crystallographic data and other structure refinement parameters of the title compound are given in Table 1. Table 2 gives the respective hydrogen bonding parameters. The ORTEP view of the molecule with atomic labeling (thermal ellipsoids drawn at 50% probability) is shown in Figure 1. Figure 2 and 3 show the packing of molecules in the crystal structure.

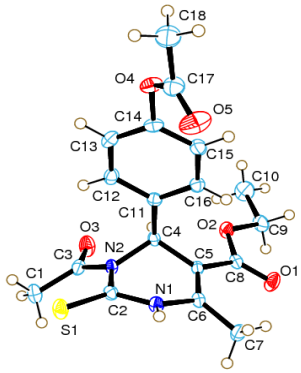


Figure 1. Ortep view of compound **2**, showing 50% Probability ellipsoids and the atom-numbering scheme.

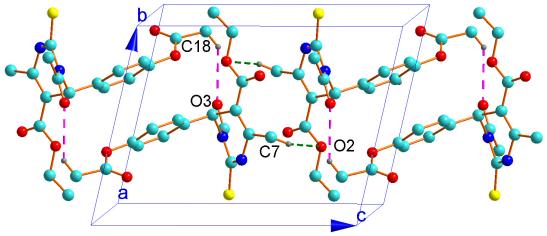


Figure 2. Packing of the molecules in crystal of **2** viewed along '*C*' axis. Dotted lines indicate C-H...O intermolecular interactions; the hydrogens are omitted for clarity.

In the title compound, the ethyl carboxylate and the methyl group lie on the left side of the dihydropyrimidine ring, whereas the acetyl and the thioxo groups are on the other side of the ring. The methoxy substituted aryl ring is positioned perpendicular to dihydropyrimidine ring[9]. The dihedral angle between the planes of the aryl and dihydropyrimidine rings is 89.65(6)°, which predisposes the molecule towards the excellent receptor-binding properties. Dihydropyrimidine of this type is known to show conformational flexibility, where as the aryl ring and the ester group can rotate and the conformation of dihydropyrimidine ring can change[10-11].

This 'aryl-group up' configuration is considered crucial for the enhanced calcium antagonist activity in this compound[12]. The 4-aryl substituent (methoxy group) adopts a synperiplanar conformation with respect to C4-H4 bond. These features have been found mandatory for optimum calcium channel modulatory activity[13]. The central dihydropyrimidine ring is significantly puckered, assuming a conformation of twisted boat similar to those, reported earlier[14]. The plane calculation shows that the atoms C4 and N2 deviate from the mean plane N1/C2/C5/C6 constituting the ring by 0.3524(2)Å and -0.2168(2)Å respectively, indicating that the conformation of the ring is that of a twisted boat, with the atoms C4 and N2 being displaced by this overall planarity of the rest of the ring. The ring puckering parameters for the dihydropyrimidine ring in the title compound are Q (2) = 0.486 (2) Å φ (2) = -16.42 (2)° and θ= 109.14 (2)° respectively.

The molecular structure is primarily stabilized by intramolecular C7-H7A…O1 hydrogen bond leading to the formation of a six-membered hydrogen bonded pattern corresponding to graph set S(6)[15] thus locking the molecular conformation and eliminating conformational flexibility. The crystal structure is further stabilized by two types of intermolecular C-H…O interactions. Both the C-H…O interaction results in the formation of head to head centrosymmetric dimers corresponding to a graph set of $R^2_2(24)$ along b' axis and $R^2_2(12)$[15] along 'c' axis respectively (Figure 2).

Additionally the crystal structure is stabilised by N-H…S intermolecular interaction resulting in the formation of dimers along 'c' axis (Figure 3). The molecular packing is further stabilized by π-π stacking interactions between the pyrimidine rings. The C5-C6 disposed at a distance of 3.825(3) Å. In addition π-ring interaction of the type C-H…Cg1 (Cg1 being the centroid of the ring C11-C16) is also observed in the crystal structure (Table 2).

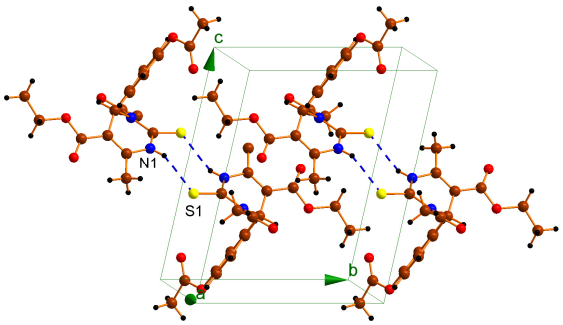


Figure 3. Packing of the molecules in crystal of **2**. Dotted lines indicate, N-H….S intermolecular interaction.

Table 2. Non-bonded interactions and possible hydrogen bonds (Å, °) for Compound **2**. (D-donor; A-acceptor; H-hydrogen)

D—H· · ·A	D—H	H· · ·A	D· · ·A	D—H· · ·A
C7-H7A...O1^{0}	0.960	2.193	2.914(2)	131
N1-H1...S1^{i}	0.860	2.569	3.366(2)	155
C7-H7B…O2^{ii}	0.960	2.818	3.645(2)	145
C18-H18B...O3^{iii}	0.960	2.769	3.571(3)	141
C10-H10B…Cg1^{iv}	0.960	2.893	3.725(4)	145

Symmetry code: (0) x, y, z (i) -x, -y, -z+1 (ii) -x, -y+1, -z+1 (iii) -x, -y+1, -z (iv) -x, 1-y, -z

Conclusion

The synthesis as well as the characterization of 4-(4-Acetoxy-phenyl)-3-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester is described. Additionally, the single crystal X-ray diffraction analysis revealed certain interesting features such as the non-planarity of the molecule, intermolecular weak interactions and supramolecular assembly.

Supplementary material

The CIF file is deposited at the Cambridge Crystallographic Data Centre, The deposition number of compound **2** is CCDC-875843.

Acknowledgement

NSB acknowledges the financial support by University Grants Commission (UGC), New Delhi, under the major research project [F-No-37-86/2009(SR)]. HN thanks UGC for the fellowship.

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